The frequency of inappropriate nonformulary medication alert overrides in the inpatient setting

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Abstract: BACKGROUND: Experts suggest that formulary alerts at the time of medication order entry are the most effective form of clinical decision support to automate formulary management. OBJECTIVE: Our objectives were to quantify the frequency of inappropriate nonformulary medication (NFM) alert overrides in the inpatient setting and provide insight on how the design of formulary alerts could be improved. METHODS: Alert overrides of the top 11 (n = 206) most-utilized and highest-costing NFMs, from January 1 to December 31, 2012, were randomly selected for appropriateness evaluation. Using an empirically developed appropriateness algorithm, appropriateness of NFM alert overrides was assessed by 2 pharmacists via chart review. Appropriateness agreement of overrides was assessed with a Cohen's kappa. We also assessed which types of NFMs were most likely to be inappropriately overridden, the override reasons that were disproportionately provided in the inappropriate overrides, and the specific reasons the overrides were considered inappropriate. RESULTS: Approximately 17.2% (n = 35.4/206) of NFM alerts were inappropriately overridden. Non-oral NFM alerts were more likely to be inappropriately overridden compared to orals. Alerts overridden with "blank" reasons were more likely to be inappropriate. The failure to first try a formulary alternative was the most common reason for alerts being overridden inappropriately. CONCLUSION: Approximately 1 in 5 NFM alert overrides are overridden inappropriately. Future research should evaluate the impact of mandating a valid override reason and adding a list of formulary alternatives to each NFM alert; we speculate these NFM alert features may decrease the frequency of inappropriate overrides.

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ABSTRACT

Background: Experts suggest that formulary alerts at the time of medication order entry is the most effective form of clinical decision support to automate formulary management.

Objective: Our objectives were to quantify the frequency of inappropriate non-formulary medication (NFM) alert overrides in the inpatient setting and provide insight on how the design of formulary alerts could be improved.

Methods: Alert overrides of the top 11 (n=206) most utilized and highest costing NFMs, from January 1st to December 31st, 2012, were randomly selected for appropriateness evaluation. Using an empirically developed appropriateness algorithm, appropriateness of NFM alert overrides were assessed by two pharmacists via chart review. Appropriateness agreement of overrides was assessed with a Cohen's kappa. We also assessed which types of NFMs were most likely to be inappropriately overridden, the override reasons which were disproportionately provided in the inappropriate overrides, and the specific reasons why the overrides were considered inappropriate.

Results: Approximately 17.2% (n=35.4/206) of NFM alerts were inappropriately overridden. Non-oral NFM alerts were more likely to be inappropriately overridden compared to orals. Alerts overridden with 'blank' reasons were more likely to be inappropriate. The failure to first try a formulary alternative was the most common reason for alerts being overridden inappropriately.

Conclusion: Approximately one in five NFM alert overrides are overridden inappropriately. Future research should evaluate the impact of mandating a valid override reason and adding a

list of formulary alternatives to each NFM alert, we speculate these NFM alert features may possibly decrease the frequency of inappropriate overrides.

INTRODUCTION

A hospital formulary is a continuously updated list of medications that represents the current clinical perspective of hospital healthcare providers for the care of admitted patients.[1] Medications on this list are generally viewed as cost-effective compared to their non-formulary alternatives, also termed non-formulary medications (NFMs). Typically, NFMs are not stocked and require special order entry and procurement procedures by the prescriber and pharmacy prior to use. These special order entry and procurement procedures can increase labor costs ($15.94 to $23.34 per order)[2-4] and can substantially delay NFM initiation (10.6 hours).[3] NFMs are also more error prone than formulary alternatives, where NFMs and their directions are more likely to be unfamiliar to hospital staff and may be misinterpreted.[5-8]

However, the need for hospitals to provide NFMs is unavoidable. Often admitted patients are stabilized on a pre-admission, chronic NFM and substitution with a formulary alternative could put the patient at risk for harm (i.e. antipsychotics and antiepileptics). Experts suggest pop-up alerts containing a list of formulary alternatives is the most effective clinical decision support (CDS) design to automate NFM management and limit the ill-effects of formulary non-compliance.[9]

Empiric verification to support this suggestion is limited. Analogous evidence can be drawn from the more commonly used computerized alerts (drug-allergy, drug-drug interactions, drug-disease contraindication, etc.), where studies have shown these alerts improve prescribing behaviors, reduce prescribing errors, impact clinical outcomes, and decrease medication cost.[10] However, these benefits are attenuate with high alert overrides frequencies (49-

96%).[11] Therefore, we are unsure if the aforementioned alert benefits are generalizable to formulary alerts.

To our knowledge, there are no studies evaluating the appropriateness of NFM alert overrides. We suspect this gap in the literature is likely due to the large variation in formularies and NFM policies from institution to institution and the resources required to create NFM alert specific appropriateness criterions for each medication not on formulary. Thus, we previously developed a 'general' appropriateness algorithm that institutions could adapt to evaluate the appropriateness of their NFM alert overrides.[12] We adapted this general algorithm to our institution's NFM use guidelines and evaluated the inappropriateness of a random sample of NFM alert overrides.

METHODS

Setting

Brigham and Women's Hospital (BWH) is a 793-bed academic medical center in Boston, MA that admits approximately 46,000 patients annually for a full range of inpatient services, with the exception of pediatrics. Both formulary and non-formulary medications are available for patient care through a computerized provider order entry (CPOE) system. Full details of BWH's CPOE system are described elsewhere.[13] Formulary alerts embedded in the CPOE system are used to automate formulary management. Upon order entry of a NFM, prescribers are informed of its non-formulary status with three types of pop-up alerts: 1) a 'soft stop' requesting the input of a free-texted override reasons, explaining the rationale of formulary deviation, 2) an 'intermediate stop' requesting a free-texted override reason and identifying the

specialist physician who approved the NFM for use, and 3) a 'hard stop' stating the NFM is not available for use and prompting the prescriber to order the preferred alternative **(Figure 1 and 2)**.

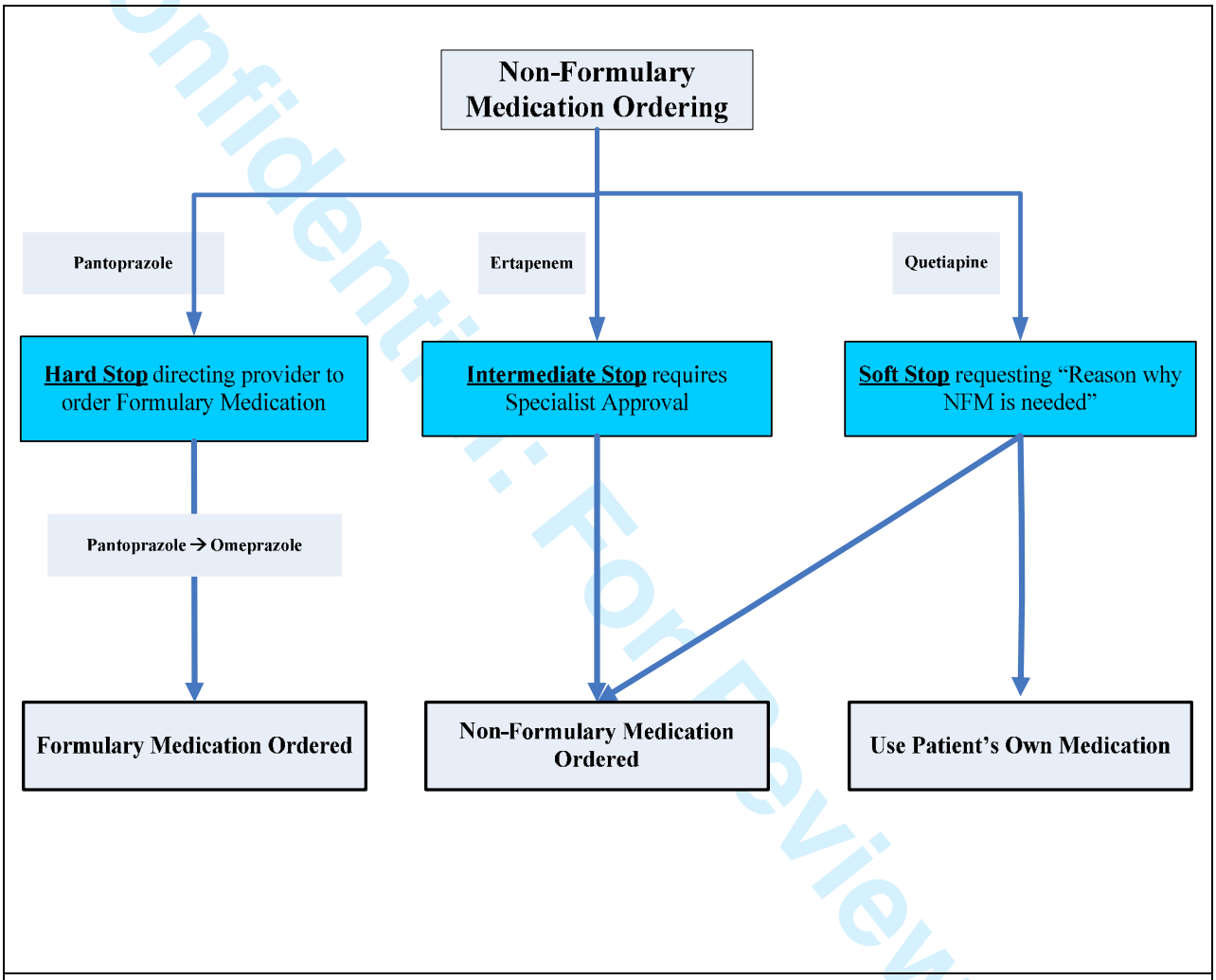
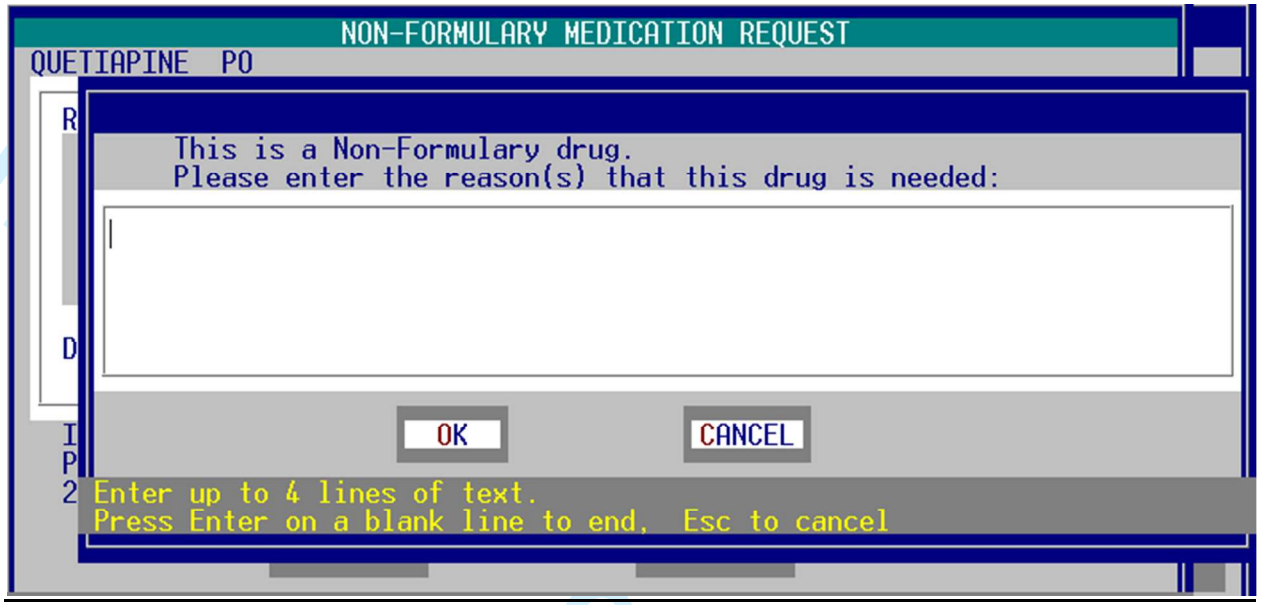


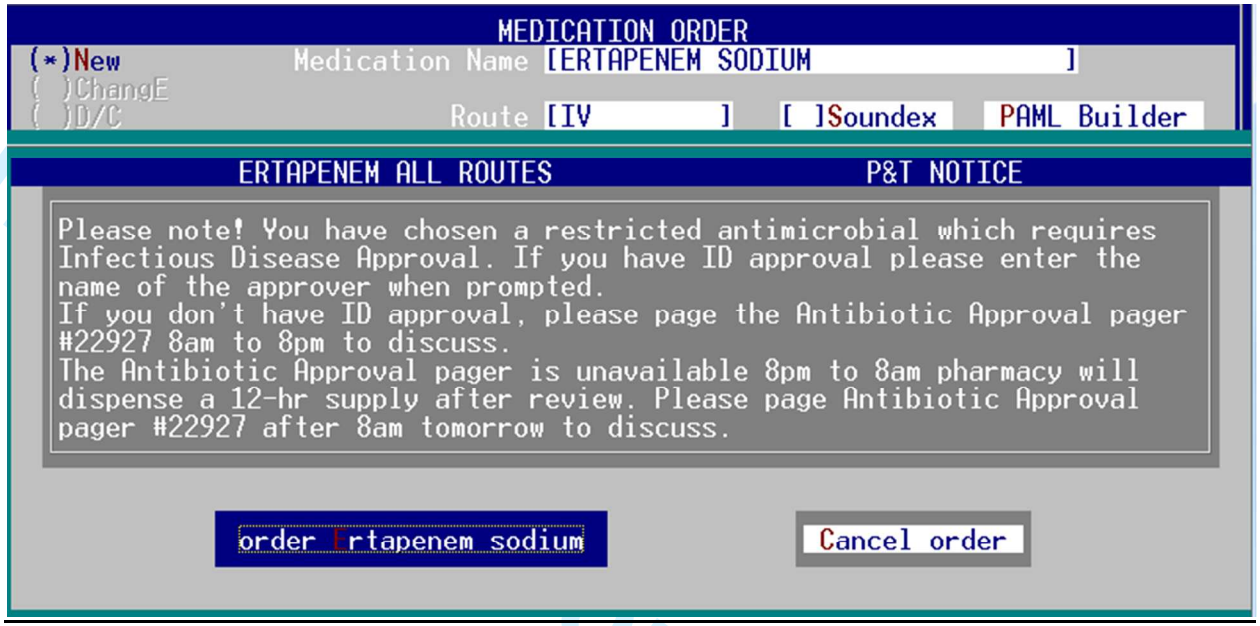
Figure 1: Non-formulary medication alerts at Brigham and Women's Hospital

Modified from Her et al, 2015[12]

A.



B.



C.

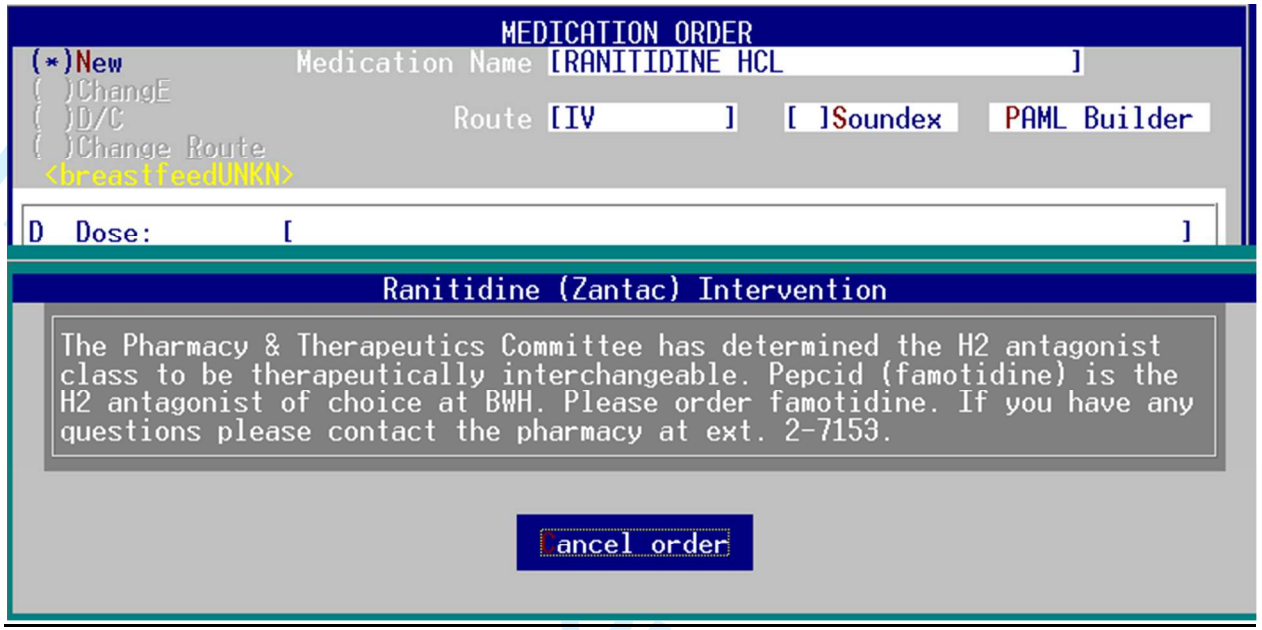


Figure 2: Non-formulary pop-up alerts

A) Soft stop, B) Intermediate stop, and C) Hard stop

Study Design and Sampling of NFM alert overrides

This observational study was conducted on all NFM alerts overridden from January 1st to December 31st, 2012. These overrides and their relevant data elements were extracted from Brigham Integrated Computer System (BICS) and loaded into a Microsoft Access Database (Microsoft Corp, Redmond, WA). Relevant data elements included patient's medical record number, patient name, admission date, discharge date, NFM order entry date, NFM order entry time, medication unique identifier, generic medication name, route, dosage, dosing frequency, prescriber name, and the free-texted NFM alert override reason.

We limited our sample of NFM alert overrides to original overrides and excluded overrides that were the result of medication dose, direction, or frequency changes. The latter overrides' rational for formulary deviation were the same as the original and including them into our evaluation would duplicate alerts. Further, at BWH there are two sources of non-formulary designation, one in BICS and the other in an online formulary dictionary. Our internal study found inconsistencies in these two sources. To ensure our evaluation included only true NFMs, we further limited our overrides sample to medications listed as non-formulary in both sources.

Total medication cost, composed of procurement and medication cost from 2009 to 2012, were computed for each NFM. The average procurement cost of providing a NFM over formulary alternatives was estimated to be $20.07 per order.[2] This estimate was used to convert the number of NFM orders to a monetary value. Medication costs were estimated from a BWH's medication wholesaler account during the first quarter of 2014. NFMs were ranked from highest to lowest total cost, and twenty alert overrides were randomly selected from the

top 11 NFMs for override appropriateness evaluation. **Figure 3** describes our NFM alert override sampling scheme.

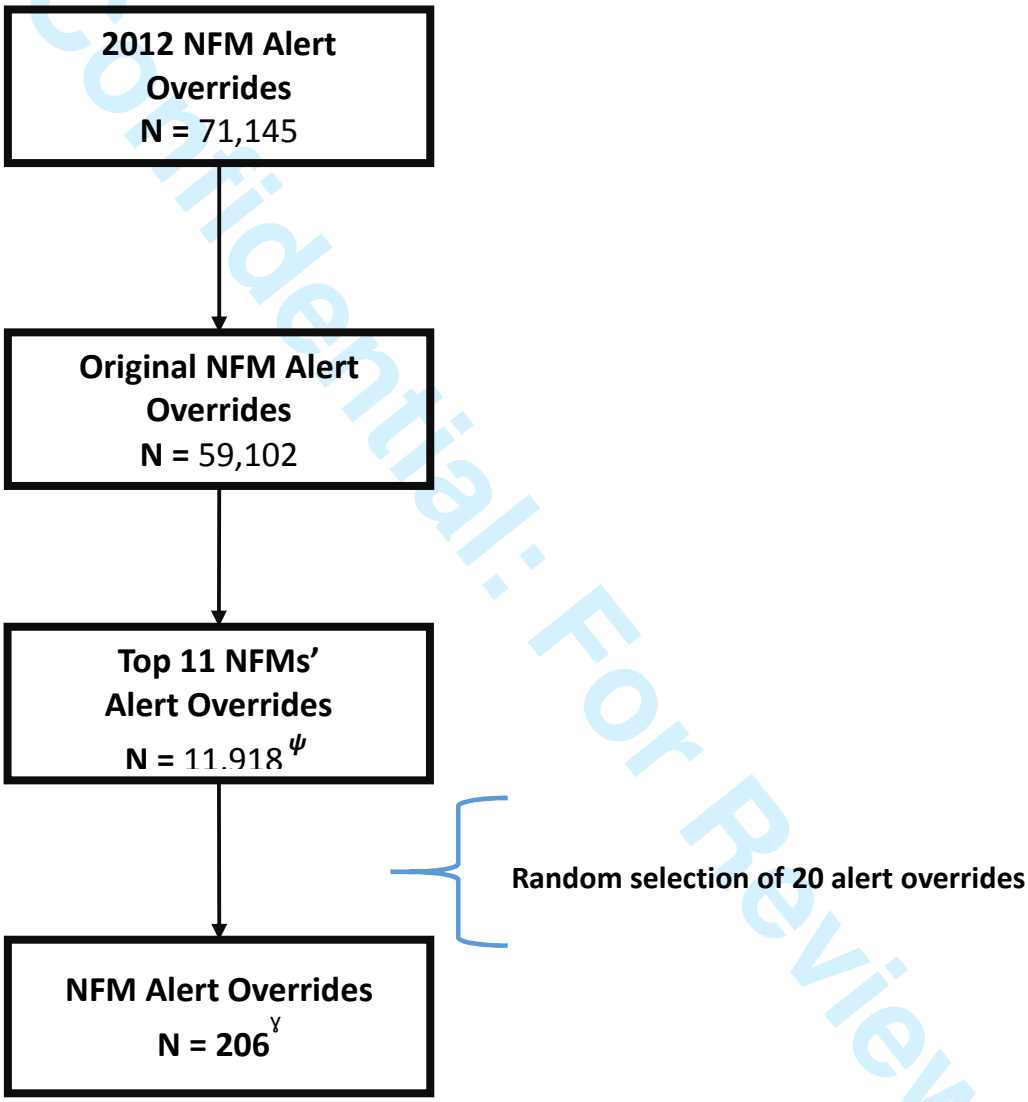


Figure 3: NFM alert override random selection

ψ Top 11 most approved and highest costing NFMs

ɣ In 2012 there were only six alert overrides for liposomal doxorubicin

NFM alert override appropriateness criteria

Previously, we empirically developed a general NFM alert override appropriateness algorithm from free-texted NFM alert override reasons. Full details of the methodology and

performance of the algorithm can be found elsewhere.[12] In brief, a NFM alert override reason categorization scheme was created from a random sample of 5,000 overrides according to keywords, context, and value explaining the rationale for formulary deviation. An initial appropriateness algorithm was developed from these override reason categories and presented to an interdisciplinary team of healthcare providers to evaluate clinical creditability and provide feedback. BWH pharmacists were also consulted and the algorithm was simplified to an eight question general appropriateness algorithm **(Figure 4)**. Available BWH medication monographs, treatment guidelines and medication administration guidelines of the top 11 NFMs were ascertained from the BWH Pharmacy intranet website and incorporated into the general algorithm to create insitution specific NFM alert override algorithms.

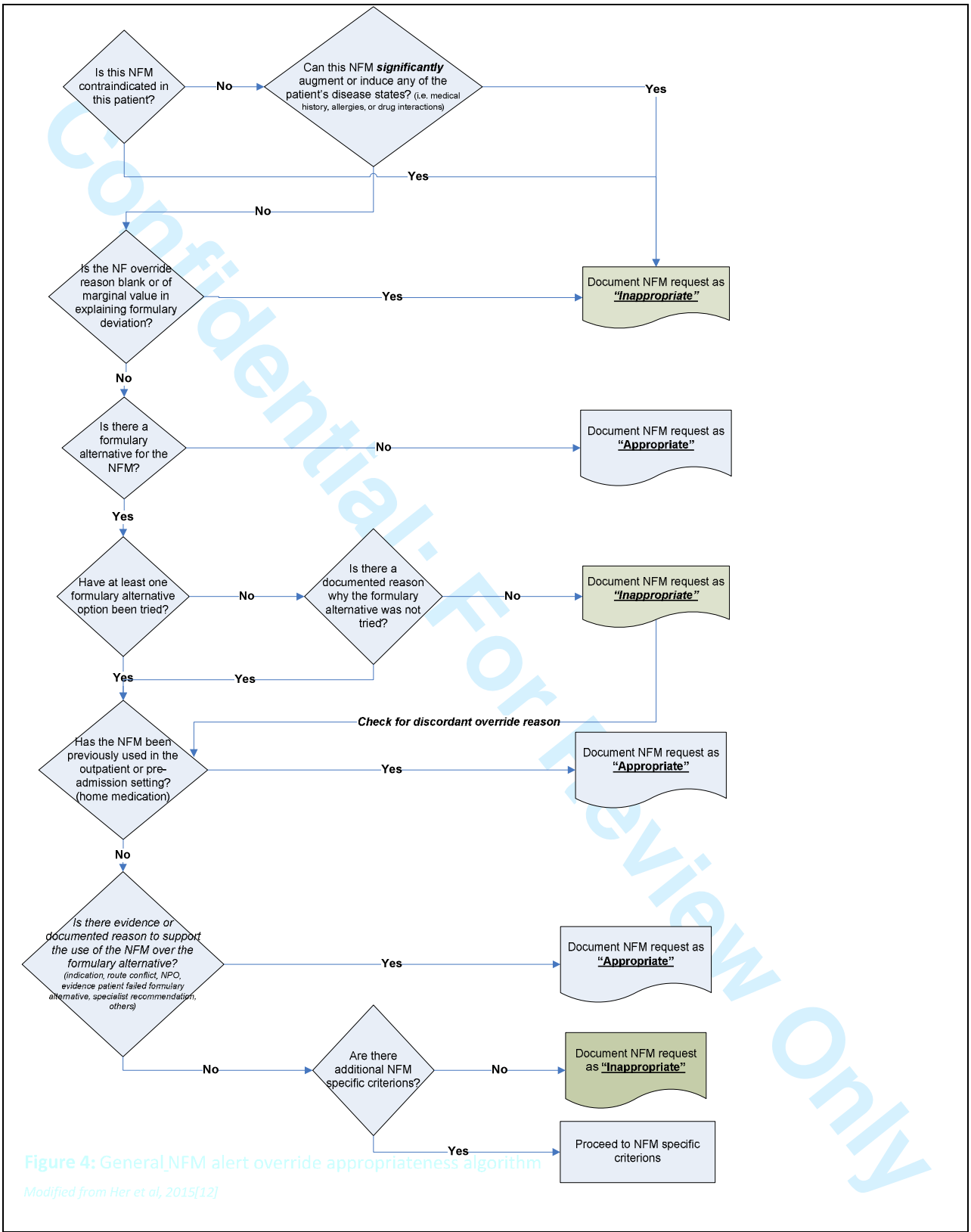


Figure 4: General NFM alert override appropriateness algorithm
Modified from Her et al, 2015[12]

Chart review and appropriateness evaluation

All inpatient notes corresponding to the hospitalization when the NFM alert was overridden were downloaded from BICS. A hyperlink to this document was created in the Microsoft Access Database to facilitate reviewer access. All medication orders and medication administration logs during hospitalization were available through BICS. Outpatient medication records were available through BWH's ambulatory care electronic medical record, Longitudinal Medical Record (LMR).

Two pharmacists (QLH and MGA) assessed the appropriateness of each NFM alert override according to the general appropriateness algorithm or NFM specific appropriateness algorithms via in-depth chart review. They first reviewed the override reason explaining the formulary deviation and identified 'preliminary' formulary alternatives to the NFM. Second, the pharmacists ensured that the NFM was not contraindicated and could not potentially induce harm to the patient according to the information found in the inpatient notes (i.e. chief complaint of admission, medical history, allergies, or drug interactions). If the NFM posed any potential harm to the patient, the NFM alert override was considered inappropriate. The reviewers also reviewed medication orders and medication administration logs for evidence of having previously tried formulary alternatives prior to the NFM alert override. The NFM alert override was considered appropriate if a formulary alternative was first tried or there was an explanation provided in the inpatient notes as to why a formulary alternative was not considered an option, otherwise the NFM alert override was considered inappropriate.

NFM alerts with 'blank' or marginal value reasons (explaining formulary deviation) were deemed inappropriate unless an appropriate justification (specialist consult, pharmacological

interaction, active disease that required the medication etc) for the NFM was discovered during chart review. NFM alert overrides justified with syntax variants of the NFM being a pre-admission or home medication were considered appropriate only if the NFM was found documented as a current medication in LMR during the dates of hospitalization or was listed in the admission history and physical note as a medication taken prior to admission. For NFMs justified by a 'disease or condition' reason, the literature was searched to ensure minimal supporting evidence existed (i.e. at least a case-report) for the proposed indication. If any evidence was found in the literature and the listed 'disease or condition' was found in the inpatient notes, then these overrides were deemed appropriate. Remaining potential reasons included specialist or pharmacist recommendation, therapeutic failure or intolerance to formulary alternatives, pharmacological reasons, end of life care, and drug shortages. These NFM alert overrides were appropriate as long as documented evidence was found in the inpatient notes. For example, olanzapine was often justified with 'per psych recommendation,' this NFM alert override would be considered appropriate if a psychiatrist consult recommending the medication was found in the inpatient notes prior the NFM being ordered. In addition, NFMs with BWH specific NFM use guidelines were considered appropriate only if they were used within those criteria. Disagreements between pharmacists were resolved by discussion with a third reviewer (DLS).

Outcomes and objectives

Our primary objective was to quantify the frequency of NFM alerts overridden inappropriately in the top 11 NFMs. Our secondary objectives were to identify which (1) types of NFMs (oral and non-oral) were most likely to be inappropriately overridden, (2) override

reasons disproportionately represent inappropriate NFM alert overrides, and (3) specific reasons why the NFM alert override was considered inappropriate. A post-hoc analysis was conducted to identify the frequency of override reason given in the NFM alert pop-up not congruent to the formulary deviation reason documented in the inpatient notes; we term these discrepancies as discordant alert override reasons.

Statistical Analysis

Counts and frequencies were used to summarize the number of inappropriate overrides according to NFM and our empirically developed NFM alert override reason categorization scheme.[12] To make overall inferences about the top 11 NFM alert overrides from our stratified random sample, post-stratification weights were computed and applied to the counts and frequencies. Weights for primary objective and secondary objective 1 were the quotients of the proportion of NFM alert overrides in the top 11 NFM alert overrides and the proportion of the NFM's alert overrides in our sample.

Post-stratification weights for secondary objective 2 were computed from our experience with an ongoing study of override reasons predictors. In brief, a random sample of 10,000 NFM (2009-12) alert overrides were extracted from BICS and their reasons were categorized according to the aforementioned reason categorization scheme by two pharmacist and a physician. Agreement in the override reason categorization between the reviewers was found to be high (κ=0.86). For the present study, we excluded all non-top 11 NFM alert overrides and the remaining constituted our auxiliary data for post-stratification weight computation. Specifically, these weights were the quotient of the proportion of override reasons in the auxiliary data and the proportion of NFM alert override reasons in our sample of

overrides **(calculations are available in the online supplementary)**. All statistical inferences were conducted on these weighted counts and frequencies.

Agreement in the inappropriateness of NFM alert overrides between the two pharmacists was evaluated with a Cohen's kappa. A chi-square test was used to compare the distribution of inappropriate NFM alert overrides among oral and non-oral NFMs. A chi-square test was also first used to determine if inappropriate NFM alert overrides were disproportionately distributed among the override reasons categories. If this latter test was found to be statistical significant, the frequency of inappropriate overrides in each override reason category was compared to the frequency of the alert override reason in our sample using a student t-test. P-values of less than 0.05 was considered to be statistically significant. A Bonferroni correction was applied to the student t-test to adjust for multiple testing. All statistical analyses were conducted using SAS software (version 9.4 SAS Institute, Cary, NC). This study was approved by the Partners Human Research Committee.

RESULTS

Table 1

Top 11 Most Approved and Highest Costing NFMs	Unweighted			Weighted			
	No. of NFM Alert Overrides	Inappropriate NFM Alert Overrides	Frequency of Inappropriate NFM Alert Override	No. of NFM Alert Overrides	Proportion of NFM Alert Overrides	No. of Inappropriate NFM Alert Overrides	Frequency of Total Inappropriate Alert Overrides
Oral non-formulary medications (n=80, 38.8%)							
Aprepitant (PO)	20	0	0.0%	7.83	60.1% (n= 123.8)	0.00	**42.8% (n= 15.18)**
Olanzapine (PO)	20	0	0.0%	19.36		0.00	
Olanzapine ODT (PO)	20	1	5.0%	27.66		1.38	
Quetiapine (PO)	20	4	20.0%	68.98		13.80	
Non-oral non-formulary medications (n= 126, 61.2%)							
Dornase Alfa (Neb)	20	4	20.0%	6.22	39.9% (n= 82.2)	1.24	**57.2% (n= 20.26)**
Liposomal Doxorubicin (IV)	6	0	0.0%	0.10		0.00	
Metronidazole 1% (Cream)	20	6	30.0%	0.76		0.23	
Mometasone Furoate (Inhaler)	20	4	20.0%	3.34		0.67	
Ranitidine (IV)	20	16	80.0%	19.48		15.58	
Rasburicase (IV)	20	0	0.0%	1.49		0.00	
Scopolamine (Patch)	20	1	5.0%	50.78		2.54	
Total	206	36	17.5%	206	100% (n= 206)	35.4 (17.2%)	

In 2012, 71,145 NFM alerts were overridden, of which 59,102 were original alert overrides for 45,352 hospitalizations. Thus, about 1.3 original NFM alerts were overridden with each hospitalization. The 11 most approved and highest costing NFMs can be found in **Table 1**. Four NFMs were oral medications, of which three were atypical antipsychotics. The remaining seven included three intravenous medications, two inhalants, and two topicals. The stratified random sample selected 206 NFM alerts overrides from these medications (there were only six liposomal doxorubicin overrides in 2012), which were prescribed by 174 distinct health care providers: 150 physicians, 21 physician-assistants, and three pharmacists.

Two (rasburicase and dornase alfa) of the 11 NFMs in our study had specific medication administration guidelines that contain 'major use' indications. Another two NFMs (scopolamine patches and aprepitant) were found in the institutions Guidelines for Assessment and Management of Nausea and Vomiting. With input from the interdisciplinary healthcare team, NFM specific criterions were created for these four NFMs (**available in online supplementary**).

According to the appropriateness algorithms, the two pharmacists found 17.2% (n=35.4) of the top 11 NFM alerts overridden inappropriately **(Table 1)**. Agreement between reviewers was high, κ=0.97 (95% CI: 0.92 – 1.00). Inappropriate alert overrides were disproportionately distributed in non-oral NFMs (p=0.021), where 57.2% (n=20.3) of inappropriate alert overrides were non-oral NFMs, but constituted only 39.9% (n=82.2) of the alert override sample **(Table 1)**.

Table 2: Non-Formulary Medication Alert Override Appropriateness Evaluation

Initiate Non-Formulary Override Reason Classification	Unweighted[1]	Weighted			
	Total No. Overrides (% of Total)	Total No. Overrides (% of Total)	Appropriate (% of Appropriate)	Inappropriate (% of Inappropriate)	P-Value[2]
Blank	**51 (24.8%)**	**44.5 (21.6%)**	**27.1 (15.7%)**	**17.5 (51.4%)**	***0.0002***
Disease or Condition Listed	**64 (31.1%)**	**68.1 (33.1%)**	**63.8 (37.1%)**	**4.3 (12.5%)**	***0.0005***
Home or Pre-Admission Medication	**38 (18.4%)**	**34 (16.5%)**	**29.5 (17.1%)**	**4.5 (13.1%)**	0.5687
Home Medication	38 (18.4%)	*33.8 (16.4%)*	*29.3 (17%)*	*4.4 (13.1%)*	
Marginal Value for NF Decision:	**30 (14.6%)**	**37.1 (18%)**	**32.2 (18.7%)**	**5 (14.6%)**	0.5685
Acknowledge NF status	2 (1%)	*3.3 (1.6%)*	*3.3 (1.9%)*	*0 (0%)*	
Content Free	1 (0.5%)	*0.9 (0.4%)*	*0.9 (0.5%)*	*0 (0%)*	
MD/Attending/Team Request, Prefers NF Medication	11 (5.3%)	*10.7 (5.2%)*	*7.8 (4.5%)*	*2.9 (8.6%)*	
MisCommunication: Medication use direction	3 (1.5%)	*1.4 (0.7%)*	*1.4 (0.8%)*	*0 (0%)*	
Others	2 (1%)	*2.9 (1.4%)*	*2.9 (1.7%)*	*0 (0%)*	
Patient Preference/Request	2 (1%)	*0.9 (0.4%)*	*0.9 (0.5%)*	*0 (0%)*	
Reason Listed "Appropriate, Effective, Indicated, Medical Necessity, No Alternative	1 (0.5%)	*3.4 (1.6%)*	*3.4 (2%)*	*0 (0%)*	
Reason Listed "Need/Requir* OR Patient Need*/Require**	8 (3.9%)	*11.3 (5.5%)*	*9.9 (5.7%)*	*1.4 (4.2%)*	
Pharmacological Reason:	**4 (1.9%)**	**3.5 (1.7%)**	**2.6 (1.5%)**	**0.9 (2.6%)**	0.6675
Contraindication	1 (0.5%)	*0.1 (0%)*	*0.1 (0.1%)*	*0 (0%)*	
Drug Route Conflict	1 (0.5%)	*2.4 (1.2%)*	*0 (0%)*	*2.4 (7.1%)*	
Others	2 (1%)	*0.8 (0.4%)*	*0.8 (0.5%)*	*0 (0%)*	
Specialist Recommendation	**10 (4.9%)**	**10.9 (5.3%)**	**9.8 (5.7%)**	**1.1 (3.2%)**	0.4753
Physician Specialist / Other Service	10 (4.9%)	*10.6 (5.1%)*	*9.5 (5.5%)*	*1.1 (3.1%)*	
Therapeutic Failure / Intolerant to formulary alternatives:	**9 (4.4%)**	**7.9 (3.8%)**	**7 (4.1%)**	**0.9 (2.6%)**	0.6796
Medication Listed	6 (2.9%)	*3.1 (1.5%)*	*3.1 (1.8%)*	*0 (0%)*	
Unspecified or Medication Not Listed	3 (1.5%)	*3.2 (1.6%)*	*2.1 (1.2%)*	*1.1 (3.1%)*	
Total	**206**	**206**	**172.02**	**33.98**	

[1]*Unweighted data and post-stratification weight computation are available in the online supplementary.*

[2]*P-values less than 0.007 (=0.05/7) were considered statistically significant, after application of a Bonferroni correction to the comparison of the proportions of inappropriate alert overrides to the proportion of overrides in each override reason category.*

288

There were 117 unique override reasons in the 206 NFM alert override sample. These reasons were categorized into 17 of the 24 previously developed override reason categories **(Table 2)**. The most common reason explaining formulary deviation of the top 11 NFMs was the provision of a 'disease or condition' (33.1%, n=68.1). No ('blank,' n=44.5) or marginal value reasons (n=37.1) were provided in 39.6% of the top 11 NFM alert overrides. 'Home or Pre-Admission Medications' reasons were used to justify 16.5% (n=34) of alert overrides and clinical reasons of pharmacological, specialist recommendation, and failure or intolerance to formulary alternatives definition explained 10.8% (n=22.3) of the NFM alert overrides.

A chi-square test confirmed a disproportionate distribution of inappropriate overrides among the categories of override reasons in our sample of alert overrides, $p< 0.001$. Specifically, subanalysis found 51.4% (n=17.5) of inappropriate overrides were nested in the 'blank' override reason category, while 'blanks' only accounted for 21.6% of appropriate alert override reasons, p=0.0002. Contrary, 12.5% of inappropriate overrides were nested in the 'disease or condition' reason category, while these reasons accounted for 33.1% of the reasons in our sample of the top NFM alert overrides, p=0.0001. Statistical analysis did not find a disproportionate number of inappropriate overrides in the remaining override reason categories **(Table 2)**.

Chart reviews identified 24 (66.7%) of the 36 inappropriate NFM alert overrides were the result of not trying formulary alternatives prior to the NFM **(Table 3)**. Eight (22.2%) of the inappropriate NFM alert overrides were justified as a pre-admission or home medication, but no evidence of active outpatient prescription was found in the patient's LMR. Chart reviews failed to find any information justifying the use of the NFMs in three (8.3%) inappropriate alert

overrides. These NFM alerts were overridden with a 'blank' or marginal value reasons (prescriber preference). Lastly, there was only one case where the NFM was deemed clinically inappropriate to the patient involving the use of an atypical antipsychotic to address dementia in an elderly patient, which has been linked to an adverse outcome.[14 15] Post-hoc analysis found 'blank' and marginal value reasons have the highest frequency of discordant override reasons, 94.1% and 93.3%, respectively **(Table 4)**.

Table 3: Reasons explaining why the NFM alert override was considered inappropriate

Non-Formulary Alert Override Reason Class	Total	Formulary alternative was not first trial prior to NFM alert override	No citation or information could be found justifying formulary deviation during chart review	Clinically Inappropriate	No evidence of active home medication found in LMR	No documentation of specialist recommendation during chart review
Blank	20	17	1	0	2	0
Disease or Condition Listed	4	4	0	0	0	0
Home or Pre-Admission Medication	5	0	0	0	5	0
Marginal Value for NF Decision: MD/Attending/Team Request, Prefers NF Medication	3	0	2	1	0	0
Marginal Value for NF Decision: Reason Listed "Need*/Requir* OR Patient Need*/Require*	1	0	0	0	1	0
Pharmacological Reason: Drug Route Conflict	1	0	0	0	0	1
Specialist Recommendation	1	1	0	0	0	0
Therapeutic Failure / Intolerant to formulary alternatives: [Unspecified or Medication Not Listed]	1	1	0	0	0	0
Total	36	23 (63.89%)	3 (8.33%)	1 (2.78%)	8 (22.22%)	1 (2.78%)

Table 4: Frequency of Discordant NFM Alert Override Reasons

Initiate Non-Formulary Override Reason Classification	Final NFM Override Reason Category (Post-Chart Review)									
	Total	**Frequency of Discordant Reason for NFM Alert Override**	**Blank**	**Disease or Condition Listed**	**Home or Pre-Admission Medication**	**Marginal Value for NF Decision:** *MD/Attending/Team Request, Prefers, NF Medication*	**Pharmacological Reason:** *Drug Route Conflict*	**Pharmacological Reason:** *Others*	**Specialist Recommendation**	**Therapeutic Failure / Intolerant to formulary alternatives:** *[Medication Listed]*
Blank	**51**	**94.1%**	**3**	**42**	**3**	**0**	**0**	**0**	**0**	**3**
Disease or Condition Listed	**64**	**7.8%**	**0**	**59**	**4**	**0**	**1**	**0**	**0**	**0**
Home or Pre-Admission Medication	**38**	**10.5%**	**0**	**1**	**34**	**0**	**0**	**0**	**3**	**0**
Marginal Value for NF Decision:	**30**	**93.3%**	**0**	**16**	**10**	**2**	**1**	**0**	**0**	**1**
MisCommunication: Medication use direction	3	100.0%	0	2	1	0	0	0	0	0
Acknowledge NF status	2	100.0%	0	1	1	0	0	0	0	0
Content Free	1	100.0%	0	1	0	0	0	0	0	0
MD/Attending/Team Request, Prefers NF Medication	11	81.8%	0	7	2	2	0	0	0	0
Others	2	100.0%	0	2	0	0	0	0	0	0
Patient Preference/Request	2	100.0%	0	0	1	0	1	0	0	0
Reason Listed "Appropriate, Effective, Indicated, Medical Necessity, No Alternative	1	100.0%	0	0	0	0	0	0	0	1
Reason Listed "Need/Requir* OR Patient Need*/Require**	8	100.0%	0	3	5	0	0	0	0	0
Pharmacological Reason:	**4**	**50.0%**	**0**	**1**	**0**	**0**	**1**	**1**	**0**	**1**
Contraindication	1	100.0%	0	1	0	0	0	0	0	0
Drug Route Conflict	1	0.0%	0	0	0	0	1	0	0	0
Others	2	50.0%	0	0	0	0	0	1	0	1
Specialist Recommendation: Specialist / Other Service Recommended	**10**	**20.0%**	**0**	**2**	**0**	**0**	**0**	**0**	**8**	**0**

Therapeutic Failure / Intolerant to formulary alternatives:	**9**	**33.3%**	**0**	**1**	**0**	**0**	**0**	**0**	**0**	**8**
Medication Listed	6	0.0%	0	0	0	0	0	0	0	6
Unspecified or Medication Not Listed	3	33.3%	0	1	0	0	0	0	0	2
Total	**206**		**3**	**122**	**51**	**2**	**3**	**1**	**11**	**13**

318

DISCUSSION

Our observational study found approximately one-fifth of NFM alert overrides in our sample of the top 11 NFMs was inappropriately overridden. Alerts of non-oral NFMs compared to oral NFMs were more likely to be inappropriately overridden. We also found NFM alerts overridden with no reason ('blank') were more likely to be inappropriately overridden, while those with 'disease or condition' reasons were less likely to be inappropriately overridden. In-depth chart review found the failure to first try a formulary alternative was the most common reason for a NFM alert override to be inappropriate. Lastly, NFM alerts overridden with 'blank' or 'marginal value' reasons often had justifiable formulary deviation reasons in the medical notes, but were poorly documented in the NFM alert pop-up interface.

To our knowledge there are no studies evaluating the appropriateness of NFM alert overrides. Thus, we are unsure of how our findings compared to other institutions. An evaluation of the appropriateness of NFM alert overrides is inherently evaluating the appropriate use of NFM. Therefore, inappropriate NFM usage frequencies may provide some estimation of the frequency of inappropriate NFM alerts overrides.

Available studies suggest the frequency of inappropriate NFM usage is approximately 60% to 70%. Specifically, a small 6-week prospective study at an academic medical center found 61% of NFM dispensed failed to comply to institution criteria[8] and a study evaluating the impact of a comprehensive formulary management system from a non structured system decreased NFM utilization from 17.8 to 5.9 medications per 100 admissions. This suggests an upper 67% bound of inappropriate NFM use.[2] Our lower frequency is likely attributed to BWH's 'relaxed'

formulary and our sample was composed of NFMs previously approved by pharmacist for use, hence also decreasing the number of inappropriate alert overrides.

Formulary Alert Design Insights

The literature on formulary CDS is scarce. Our secondary findings provide important perspectives on how to prioritize and possibly improve the design of alerts for automated formulary management. First, alert improvement and optimization should be a prioritize to non-oral NFMs. Non-oral NFMs have greater cost-implications than oral NFMs. Sweet et al estimated the successful conversion of non-oral NFMs to a formulary alternative saves between $7.04 to $94.60 compared to only $16.62 in oral NFMs.[4] Our study found non-oral NFM alert overrides were more likely to be inappropriate compared to oral NFMs. Thus, optimization of automated formulary management with non-oral NFMs is more likely to yield formulary cost-savings.

Second, it is not surprising that the provision of no reason ('blank') to NFM alerts overrides were disproportionately inappropriate. This is to be likely reflective of BWH's 'relaxed' formulary, but also a characteristic of volunteer free-texted alert systems.[16] Mandating the provision of an override reason may decrease the frequency of inappropriate NFM alert overrides, hence inappropriate NFM use.

Third, we expected the NFM alerts overridden with clinical reasons (pharmacological, specialist recommendation, and therapeutic failure / intolerant to formulary alternatives) more likely to be appropriate, but were only able to demonstrate this relationship with alerts overridden with 'disease or condition' reasons. The inability to demonstrate this hypothesis

with the former clinical reasons is likely due to their small numbers in our sample. Our previous study found clinical reasons were rarely entered into our alert system,[12] which is surprising with our sampling being composed of only approved NFM overrides. Post-hoc analysis and chart review found nearly all NFM alerts overridden with 'blank' (45 of the 51) or 'marginal value' (28 of the 30) reasons could have been overridden with clinical reasons **(Table 4)**. Our chart review found a large number of these overrides contained 'disease or condition' rationale for NFM usage (58 of the 81) and appropriate (57 of the 81), but justification was poorly documented in the NFM alert pop-up window. This is consistent with our findings that NFM alerts overridden with 'disease or condition' reasons are likely to be appropriate. Thus, we speculate mandating the provision of a valid override reason may possibly shift the behavior of providing of 'blank' and 'marginal value' reasons to 'disease or condition' reasons, hence possibly decreasing the frequency of inappropriate NFM alert overrides.

Fourth, chart review found inappropriate NFM alert overrides were largely attributed to prescriber not trying formulary alternatives prior to the NFM. This is likely to be due to BWH's large number of NFMs managed by a soft stop, where guidance to formulary alternatives is not provided. Listing formulary alternatives in the pop-up alerts may facilitate the use and trial of formulary alternatives, hence decreasing the frequency of inappropriate NFM alert overrides. A recent study found an obtrusive, hard-stop, pop-up alert prompting formulary interchange decreased formulary non-adherence by 65%.[17] In addition a list of formulary alternatives that is clear, concise, and includes links to additional information may also further decrease the frequency of inappropriate NFM alert overrides.[11 18-20]

Limitations

Our study has a number of limitations. First, our study was retrospective, thus we were limited to the information documented in the inpatient notes and administrative data. There were three 'blank' overrides where no information regarding the rationale of NFM use was found and numerous incidences where 'blank' overrides were actually justified after chart review. This leads us to infer that prescribers could have discussed appropriate rationale for NFM alert overrides during patient care rounds with the team, specialist, or rounding pharmacist, but failed to document appropriately. Therefore, the aforementioned three 'blank' overrides may have been appropriate, but just not appropriately documented, decreasing our frequency of inappropriate override to 16.0%.

Second, our study was undertaken at a single medical center with an in-house developed CPOE system and utilized appropriateness criteria specific to one institution. Thus the quantitative results may not be fully generalizable to other institutions and medication ordering system. Nevertheless, our study provide important design perspectives on computerized formulary management systems and formulary-based alerts, which may be considered to further ensure formulary cost-savings, quality of care, and medication safety. In addition, with the application of empirically developed general appropriateness criteria to an automated formulary management system our study may serve as a model for future formulary-based CDS studies.

Lastly, our analysis focused on only a subset of NFM alert overrides, the most approved and highest costing NFMs. It is possible our findings may have differed with the inclusion of all NFMs. However, such a study is likely infeasible due to the need to create alert override appropriateness criteria for each NFM. Our decision to focus on the highest cost and most

approved NFMs was to identify insight that may yield the greatest improvement in the use of alerts for formulary management.

CONCLUSION

To our knowledge, our study is the first to empirically evaluate the appropriateness of NFM alerts overrides in the inpatient setting. This is a labor-intensive task and requires the creation of appropriateness criteria for each NFM. We circumvented this issue by tailoring an empirically developed NFM alert override general appropriateness algorithm to our institution's NFM use guidelines and focused on the most approved and high costing NFMs. This study conservatively estimated that one in five NFM alert overrides were inappropriately overridden. Future research should evaluate the impact of mandating a valid override reason and adding a list of formulary alternatives to each NFM alert, we speculate these NFM alert features may possibly decrease the frequency of inappropriate NFM alert overrides, especially in those overridden with a 'blank' or 'marginal value' reason.

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Contributorship Statement: DWB, QLH, MGA, and DLS contributed to the conception and design, acquisition of data, data manipulation, analysis and interpretation. QLH led the drafting of the manuscript and revising it for critical important intellectual content. QLH and MGA had

access to all data and take responsibility for the integrity and accuracy and analysis of the data. PEB, SPS, OD, PCD, JFG, and JF contributed to the conception and design, drafting of the manuscript or revising it for critical important intellectual content. JMF contributed to the acquisition of data and technical or material support. All authors commented on manuscript drafts and gave their approval for the final version to be published. DWB obtained funding and was responsible for supervision of all activities.

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Table 1

	Unweighted			Post-Stratification Weight Computations						
Top 11 Most Approved and Highest Costing NFMs	**No. of NFM Alert Overrides**	**Inappropriate NFM Alert Overrides**	**Alert Override Population (N = 11,918)**	**Proportion of Alert Override Population**	**Proportion of Alert Override Sample**	**Post-Stratification Weights**	***Weighted* No. of NFM Alert Overrides**	**Proportion of NFM Alert Overrides**	***Weighted* No. of Inappropriate NFM Alert Overrides**	**Frequency of Total Inappropriate Alert Overrides**
	N_i	X_i		P_{AOP_i}	P_{AOS_i}	$\frac{P_{AOP_i}}{P_{AOS_i}}$	$\frac{P_{AOP_i}}{P_{AOS_i}} * N_i$		$\frac{P_{AOP_i}}{P_{AOS_i}} * X_i$	
Oral non-formulary medications (n=80, 38.8%)										
Aprepitant (PO)	20	0	453	0.04	0.10	0.39	7.83	60.1% (n= 123.8)	0.00	**42.8% (n= 15.18)**
Olanzapine (PO)	20	0	1120	0.09	0.10	0.97	19.36		0.00	
Olanzapine ODT (PO)	20	1	1600	0.13	0.10	1.38	27.66		1.38	
Quetiapine (PO)	20	4	3991	0.33	0.10	3.45	68.98		13.80	
Non-oral non-formulary medications (n= 126, 61.2%)										
Dornase Alfa (Neb)	20	4	360	0.03	0.10	0.31	6.22	39.9% (n= 82.2)	1.24	**57.2% (n= 20.26)**
Liposomal Doxorubicin (IV)	6	0	6	0.00	0.03	0.02	0.10		0.00	
Metronidazole 1% (Cream)	20	6	44	0.00	0.10	0.04	0.76		0.23	
Mometasone Furoate (Inhaler)	20	4	193	0.02	0.10	0.17	3.34		0.67	
Ranitidine (IV)	20	16	1127	0.09	0.10	0.97	19.48		15.58	
Rasburicase (IV)	20	0	86	0.01	0.10	0.07	1.49		0.00	
Scopolamine (Patch)	20	1	2938	0.25	0.10	2.54	50.78		2.54	
Total	206	36	11918	1.00	1.00	10.31	206	100% (n= 206)	35.4	

Table 2: Non-Formulary Medication Alert Override Appropriateness Evaluation

Initiate Non-Formulary Override Reason Classification[1]	Unweighted[2]			Post-Stratification Weights Computation				Weighted		
	Total	App Overrides	Inapp Overrides	Auxiliary Data	Proportion of Auxiliary Data	Proportion of Sample	Weights	Total	App Overrides	Inapp Overrides
	N_i	Y_i	X_i		P_{A_i}	P_{S_i}	$\frac{P_{A_i}}{P_{S_i}}$	$\frac{P_{A_i}}{P_{S_i}} * N_i$	$\frac{P_{A_i}}{P_{S_i}} * Y_i$	$\frac{P_{A_i}}{P_{S_i}} * X_i$
Blank	**51**	**31**	20	**446**	**0.216**	**0.248**	**0.873**	**44.54**	**27.07**	**17.46**
Disease or Condition Listed	**64**	**60**	4	**682**	**0.331**	**0.311**	**1.064**	**68.10**	**63.84**	**4.26**
Home or Pre-Admission Medication	**38**	**33**	5	**340**	**0.165**	**0.184**	**0.893**	**33.95**	**29.48**	**4.47**
Home Medication	38	*33*	5	338	*0.164*	*0.184*	*0.888*	*33.75*	*29.31*	*4.44*
Transfer from an outside hospital	*0*	*0*	*0*	2	*0.001*	*0.000*	UND	UND	UND	UND
Marginal Value for NF Decision:	**30**	**26**	**4**	**372**	**0.180**	**0.146**	**1.238**	**37.15**	**32.19**	**4.95**
Acknowledge NF status	2	2	0	33	*0.016*	*0.010*	*1.648*	*3.30*	*3.30*	*0.00*
Content Free	1	1	0	9	*0.004*	*0.005*	*0.899*	*0.90*	*0.90*	*0.00*
End of life care, Comfort measure only	*0*	0	0	24	*0.012*	*0.000*	UND	UND	UND	UND
MD/Attending/Team Request, Prefers NF Medication	11	8	3	107	*0.052*	*0.053*	*0.971*	*10.68*	*7.77*	*2.91*
MisCommunication: Medication use direction	3	3	0	14	*0.007*	*0.015*	*0.466*	*1.40*	*1.40*	*0.00*
Others	2	2	0	29	*0.014*	*0.010*	*1.448*	*2.90*	*2.90*	*0.00*
Patient Preference/Request	2	2	0	9	*0.004*	*0.010*	*0.449*	*0.90*	*0.90*	*0.00*
Reason Listed "Appropriate, Effective, Indicated, Medical Necessity, No Alternative	1	1	0	34	*0.016*	*0.005*	*3.395*	*3.40*	*3.40*	*0.00*
Reason Listed "Need/Requir* OR Patient Need*/Require**	8	7	1	113	*0.055*	*0.039*	*1.410*	*11.28*	*9.87*	*1.41*
Pharmacological Reason:	**4**	**3**	**1**	**35**	**0.017**	**0.019**	**0.874**	**3.49**	**2.62**	**0.87**
Allergy	*0*	*0*	*0*	1	*0.000*	*0.000*	UND	UND	UND	UND
Contraindication	1	1	0	1	*0.000*	*0.005*	*0.100*	*0.10*	*0.10*	*0.00*
Drug Route Conflict	1	0	1	24	*0.012*	*0.005*	*2.397*	*2.40*	*0.00*	*2.40*
Drug Shortage	*0*	0	0	1	*0.000*	*0.000*	UND	UND	UND	UND
Others	2	2	0	8	*0.004*	*0.010*	*0.399*	*0.80*	*0.80*	*0.00*
Specialist Recommendation	**10**	**9**	1	**109**	**0.053**	**0.049**	**1.088**	**10.88**	**9.80**	**1.09**
Physician Specialist / Other Service	*10*	9	1	106	*0.051*	*0.049*	*1.058*	*10.58*	*9.53*	*1.06*
Pharmacist	*0*	*0*	*0*	3	*0.001*	*0.000*	UND	UND	UND	UND
Therapeutic Failure / Intolerant to formulary alternatives:	**9**	**8**	**1**	**79**	**0.038**	**0.044**	**0.877**	**7.89**	**7.01**	**0.88**
Medication Listed	6	6	0	31	*0.015*	*0.029*	*0.516*	*3.10*	*3.10*	*0.00*

Unspecified or Medication Not Listed	3	2	1	32	*0.016*	*0.015*	*1.065*	*3.20*	*2.13*	*1.07*
NFM effective or tolerated in the past	*0*	*0*	*0*	16	*0.008*	*0.000*	*UND*	*UND*	*UND*	*UND*
Total	**206**	**170**	**36**	**2063**	**1**			**206**	**172.02**	**33.98**

[1] *Override categories that were not found in our stratified random sample, but in our auxiliary data had undefined weights, as the denominator was zero. These override reasons did not contribute to our analysis, but are needed for post-stratification weight computations.*

[2] *Unweighted data and post-stratification weight computations are available in the online supplementary.*

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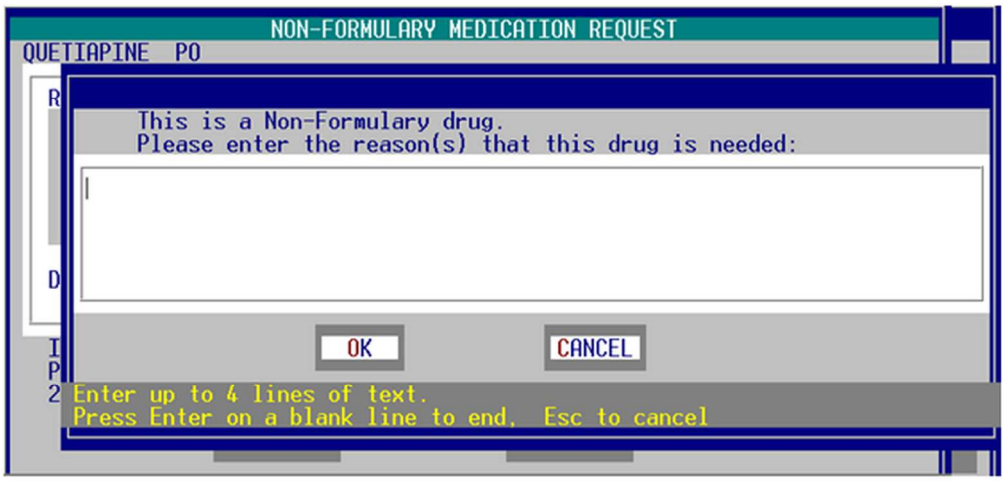

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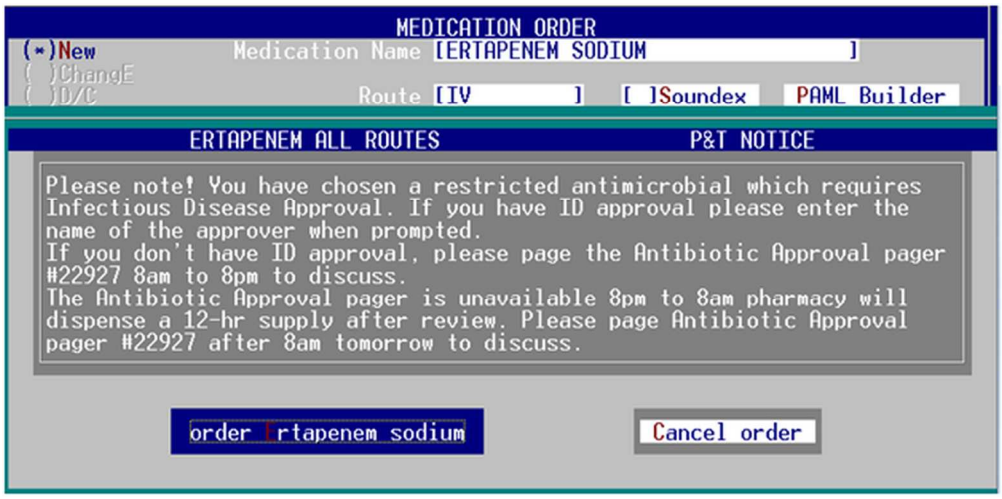

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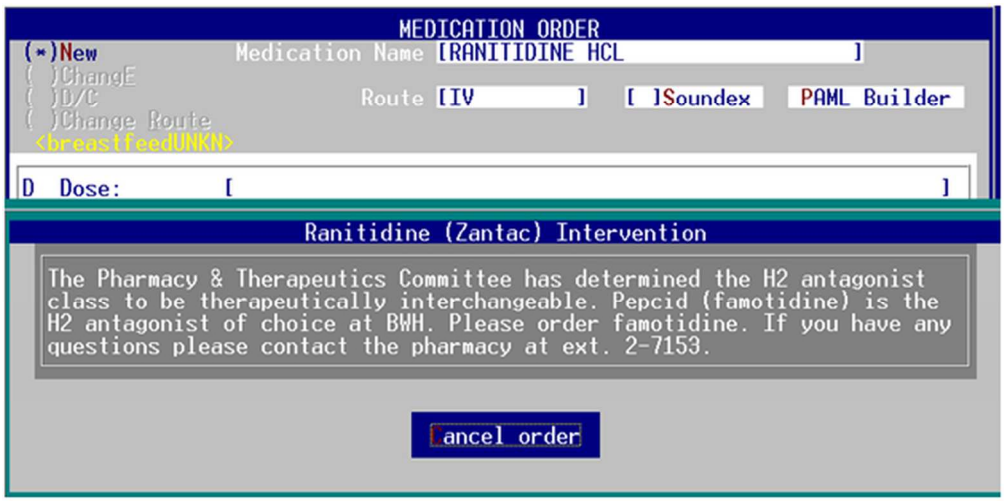

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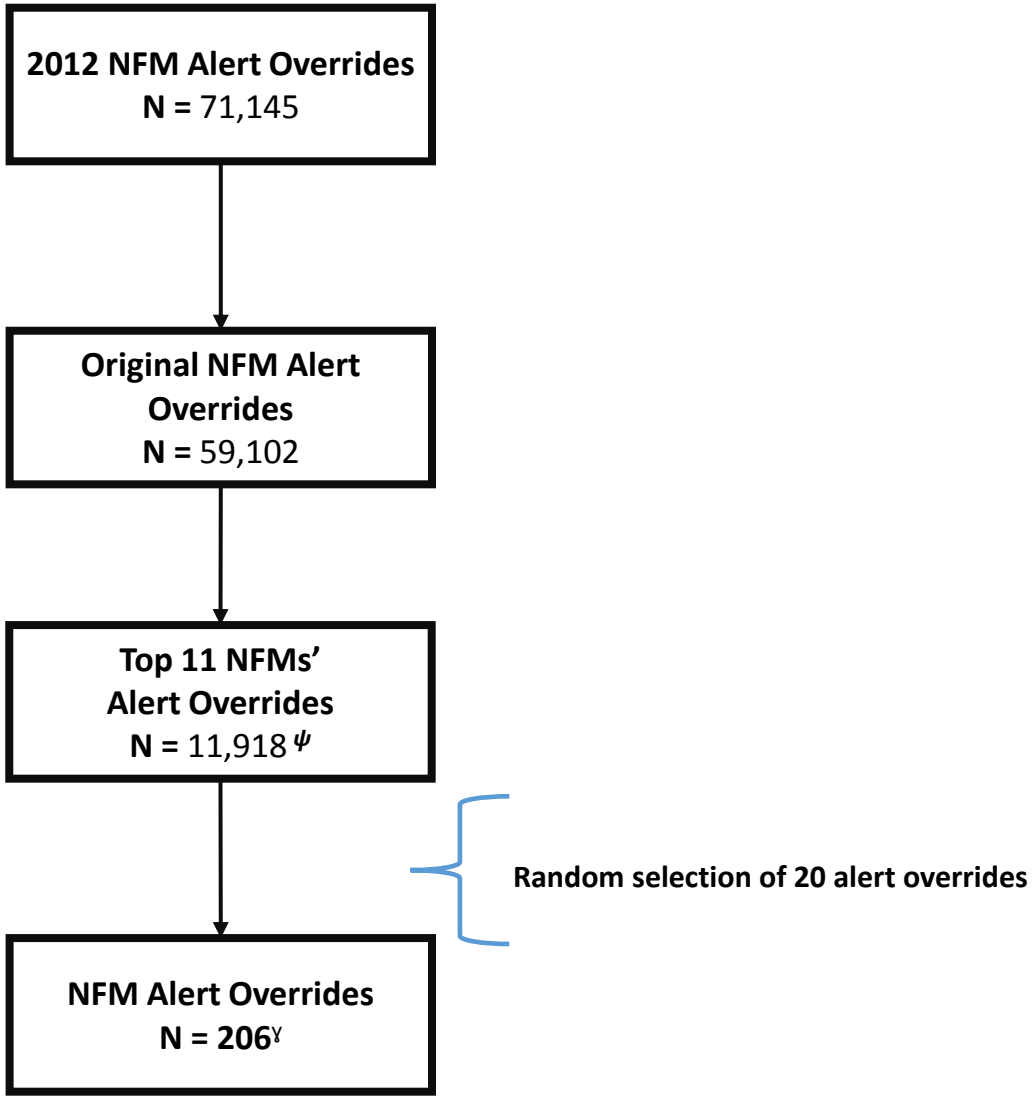

Figure 3: NFM alert override random selection

ψTop 11 most approved and highest costing NFMs

ɣIn 2012 there were only six alert overrides for liposomal doxorubicin

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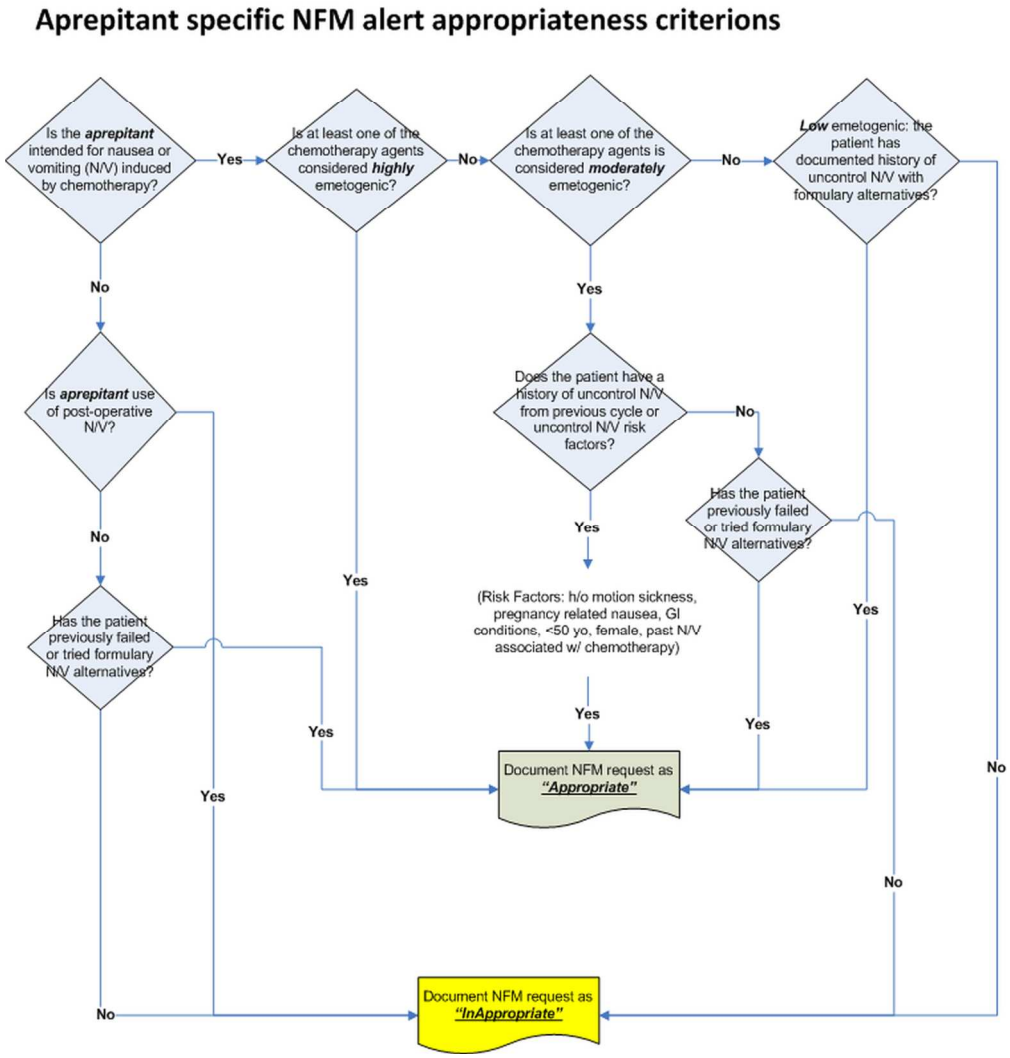

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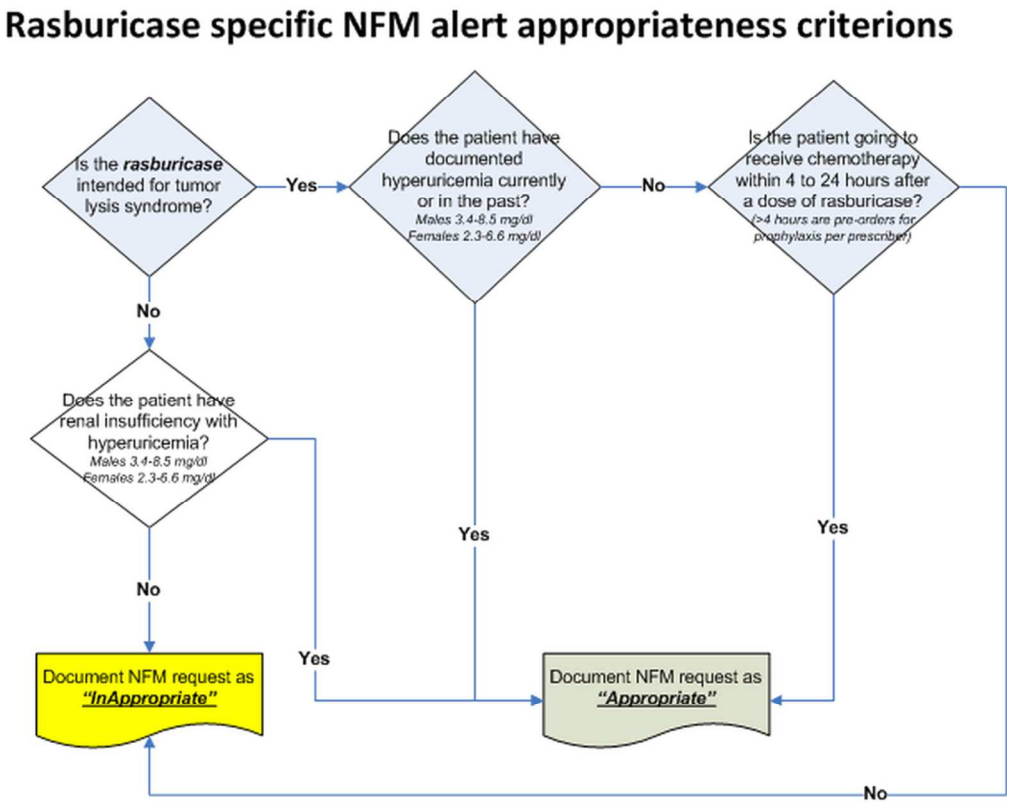

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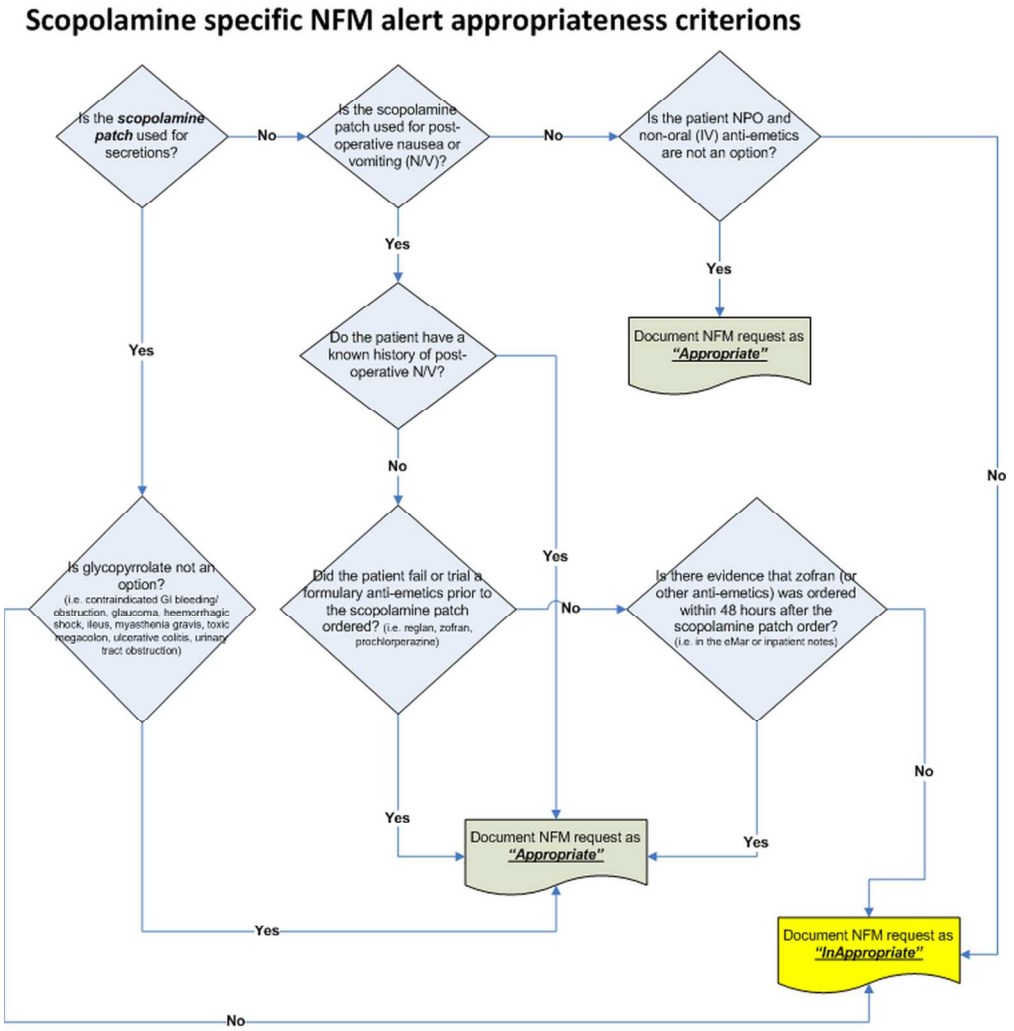
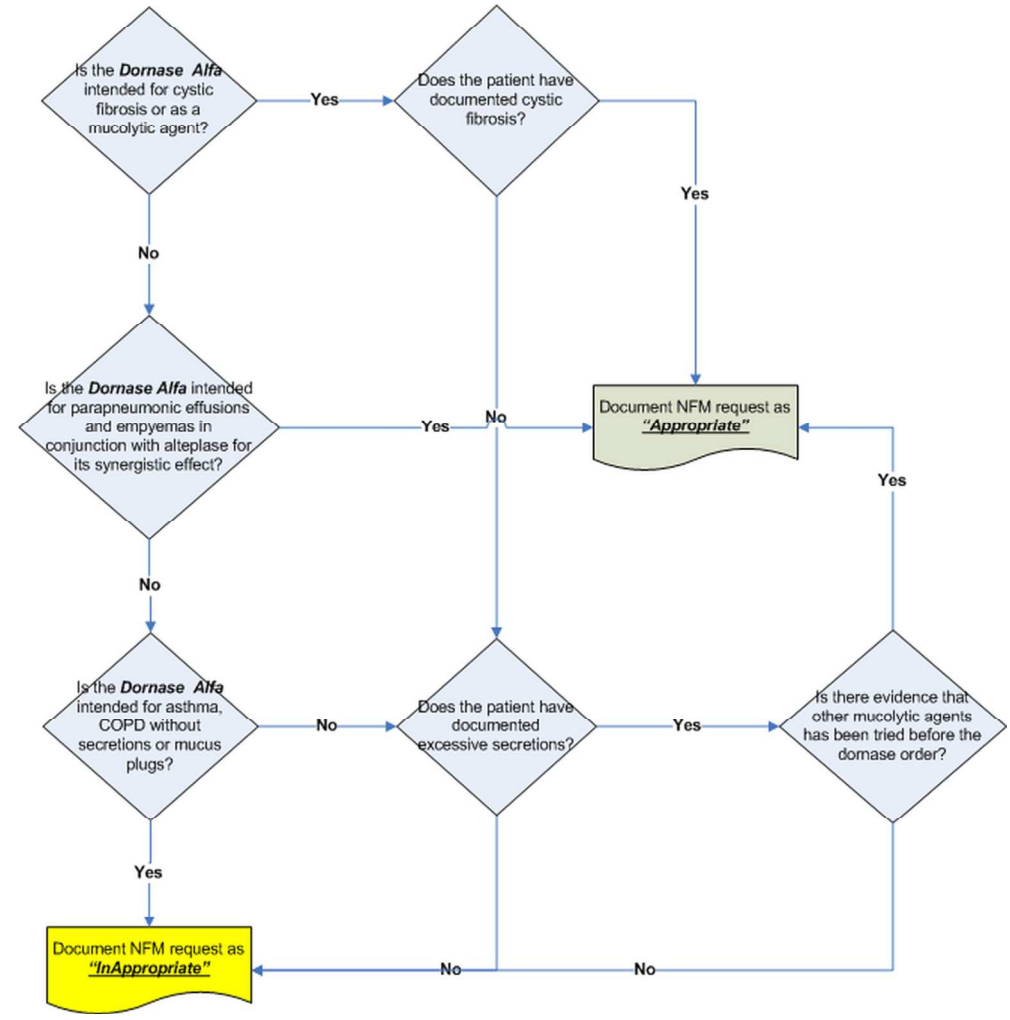


78x81mm (600 x 600 DPI)



82x89mm (600 x 600 DPI)